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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/687,709	10/20/2003	Shigeru Kawahara	242579US0CONT	2840

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EXAMINER	
PRATS, FRANCISCO CHANDLER	
ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 09/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/687,709	KAWAHARA ET AL.	
	Examiner	Art Unit	
	Francisco C Prats	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *32 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-20-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1651.

Claims 1-34 are presented for examination.

Election/Restrictions

Applicant's election with traverse of the group IV invention in the reply filed on July 15, 2004 is acknowledged.

The traversal is on the ground(s) that that the restriction is improper because all of the various inventions are related by dependency. This is not accurate. Claims 19-25 and 31 do not depend from any other claims, and lack the allegedly critical first step of formylating aspartic acid recited in claim 1. Thus, in addition to lacking the feature alleged in the specification as providing a critical distinction over the prior art, claims 19-25 and 31 clearly recite a process materially different than that recited in the remaining claims. Also, the process recited in claim 1 does not have any steps in common with the processes recited in claims 19-25 and 31, and the two processes yield different products. Further still, the process

of claim 31 does not have any of the process steps recited in claims 19-25.

Similarly, claims 32 and 33 do not depend from any other claims. Moreover, the formyl derivatives of neutral amino acids produced in claims 32 and 33 are entirely different compounds than the formyl derivative of aspartic acid or methyl ester of phenylalanine required in the other pending claims. In fact, the formyl derivatives of neutral amino acids recited in claims 32 and 33 cannot possibly be used in the synthetic methods recited in the other claims, since an entirely different product would result. Thus, claims 32 and 33 are clearly unrelated to the remaining claims, as asserted in the original restriction requirement.

Further still, as to burden, claims 32 and 33 encompass the preparation formyl derivatives of any neutral amino acid, of which there are more than a few. Therefore, because claims 32 and 33 require the search and examination of a plurality of compounds entirely different than the compounds recited in the remaining claims, it is clear that examination of claims 32 and 33 presents a significant burden on the search and examination processes.

Lastly, note that it is simply incorrect to assert that claims related by dependency cannot be restricted. No rule or law supports that proposition.

The requirement is still deemed proper and is therefore made FINAL.

In view of the prior art encountered during search of the elected invention, the restriction requirement has been withdrawn with respect to all claims except claims 32 and 33. Claims 32 and 33 are therefore withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. As discussed immediately above, applicant timely traversed the restriction (election) requirement in the reply filed on July 15, 2004.

Claims 1-31 and 34 are examined on the merits.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Carter (U.S. Pat. 4,789,757).

Carter describes a process of preparing N-formyl-aspartic acid by reacting aspartic acid with formamide. See, e.g., Example 1, at columns 2 and 3. Note that formamide is a base. Thus, Carter describes reacting aspartic acid with formamide, in the presence of a base, formamide, as recited in the claim. A holding of anticipation is therefore required.

Claims 1 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Quirk et al (U.S. Pat. 4,801,742).

Quirk describes a process of preparing N-formyl-aspartic acid by reacting aspartic acid with methyl formate in the presence of sodium methoxide. See, e.g., Examples 5, 7-10, 15 and 16, at columns 5-7. Note that sodium methoxide is a base. Thus, Quirk describes reacting aspartic acid with methyl formate, in the presence of a base, as recited in the claims. A holding of anticipation is therefore required.

Claims 19, 20, 22, 24, 25 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Likos et al (EP 0 149 594).

Likos describes a method of preparing N-formyl-α-L-aspartyl-L-phenylalanine methyl ester wherein 10 mmol of N-formyl-L-aspartic acid is placed into a 5 mL reaction mixture (a 2 M solution) along with thermolysin, a protease enzyme, and an L-phenylanine methyl ester, resulting in a 1:1 addition product (adduct) of N-formyl-α-L-aspartyl-L-phenylalanine methyl ester and L-phenylanine methyl ester. See Example 2 on page 11. Likos describes that this product can be converted to aspartame by removal of the formyl group, as recited in claims 24 and 25. See, e.g., reaction scheme depicted at pages 5 and 6. Lastly, with respect to claim 31, note specifically that Likos in fact discloses a process wherein the adduct is suspended in an aqueous solution of pH 1.6. See Example 1 on page 10. A holding of anticipation over the cited claims is clearly required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19-21 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Likos et al (EP 0 149 594).

Likos describes a method of preparing N-formyl-α-L-aspartyl-L-phenylalanine methyl ester wherein 10 mmol of N-formyl-L-aspartic acid is placed into a 5 mL reaction mixture (a 2 M solution) along with thermolysin, a protease enzyme, and an L-phenylanine methyl ester, resulting in a 1:1 addition product (adduct) of N-formyl-α-L-aspartyl-L-phenylalanine methyl ester and L-phenylanine methyl ester. See Example 2 on page 11.

Likos differs from the claims in that Likos does not contain a single embodiment wherein the concentration of N-formyl-L-aspartic acid is greater than 1.2 M ***and*** the adduct is suspended in a pH 1.0 to 4.5 aqueous solution for recovery, as

recited in claim 21. However, from Example 2 of Likos it is clear that a concentration of N-formyl-aspartic acid greater than 1.2 M was suitable in the enzymatic condensation reaction. Moreover, from Example 1 of Likos it is also clear that the claimed adduct recovery method was a suitable recovery method. Thus, the claimed selection of recovery methods and reagent concentrations disclosed in the prior art as being suitable for the disclosed processes must be considered obvious under § 103(a). That is, the artisan of ordinary skill would have been motivated to have used the parameters disclosed by Likos as being suitable methods of achieving the disclosed results.

Likos also differs from the claims in that Likos does not contain a single embodiment wherein the concentration of N-formyl-L-aspartic acid is greater than 1.2 M and the pH of the condensation reaction is 6 to 8. However, in view of the examples' use of pH's of 6.5, 5.8, and 6.6, the artisan of ordinary skill clearly would have been motivated to have conducted the protease-catalyzed condensation reaction at the claimed pH values when using a concentration of N-formyl-aspartic acid of greater than 1.2

Claims 2-4 and 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Likos et al (EP 0 149 594) in view of

Carter (U.S. Pat. 4,789,757) and Quirk et al (U.S. Pat. 4,801,742).

As discussed above, Likos describes a method of preparing N-formyl-α-L-aspartyl-L-phenylalanine methyl ester wherein 10 mmol of N-formyl-L-aspartic acid is placed into a 5 mL reaction mixture (a 2 M solution) along with thermolysin, a protease enzyme, and an L-phenylanine methyl ester, resulting in a 1:1 addition product (adduct) of N-formyl-α-L-aspartyl-L-phenylalanine methyl ester and L-phenylanine methyl ester. See Example 2 on page 11.

While Likos discloses that formylation of the aspartic acid is part of the overall process (see reaction scheme depicted at pages 5 and 6), Likos differs from the claims in that Likos does not disclose that the N-formyl-L-aspartic acid is prepared by reacting aspartic acid with methyl formate or formamide in the presence of base. However, as also discussed above, Carter and Quirk disclose that those methods were suitable for preparing formylated aspartic acid. In particular each of Carter (e.g. column 2, lines 55-57) and Quirk (e.g. column 4, lines 12-31) discloses that the formyl-aspartic acid produced therein is suited for use in the production of dipeptides, including aspartame, and that the processes were advantageous in various aspects including yield and simplicity of use. See, e.g.,

Carter at column 1, lines 45-48; see also Quirk at column 1, lines 60-67. Thus, the artisan of ordinary skill practicing Likos' method of preparing aspartame and intermediates thereof clearly would have been motivated to have used the methods of Carter and/or Quirk to have prepared the formyl-aspartic acid starting material required in Likos' methods by the direct suggestions in Carter and Quirk of the suitability of their products in such syntheses, and by the described advantages. A holding of obviousness is clearly required.

Claims 2-18, 26-30 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Likos et al (EP 0 149 594) in view of Carter (U.S. Pat. 4,789,757) and Quirk et al (U.S. Pat. 4,801,742) as applied to claims 2-4 and 10-13 above, and further in view of Hirata (U.S. Pat. 5,837,483).

As discussed above, Likos, when taken in view of Carter and Quirk, renders obvious the enzymatic preparation of aspartame and its intermediates from formyl-aspartic acid produced by the claimed methods. Likos, Carter an Quirk differ from the claims in not disclosing the use of trialkyl phosphate in the condensation reaction as recited in the claims. However, Hirata clearly discloses that the use of water-immiscible solvents, including tributyphosphate, are advantageous in the enzymatic

synthesis of aspartame and its intermediates, in that yields are optimized. See, e.g. Example 3 at columns 8 and 9. Thus, the artisan of ordinary skill, recognizing from Hirata the advantages of using a trialkyl phosphate in the enzymatic reaction medium of Likos, clearly would have been motivated to have used Hirata's improvement so as to obtain the improved yield disclosed by Hirata as resulting from the process.

In sum, on the current record the cited claims recite processes comprising variations known to be advantageous in the art of preparing aspartame by enzymatic condensation. A holding of obviousness is therefore required.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Francisco C Prats whose telephone number is 571-272-0921. The examiner can normally be reached on Monday through Friday, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G Wityshyn can be reached on 571-272-0926. The fax phone number for the

organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Francisco C Prats
Primary Examiner
Art Unit 1651

FCP